

P1 1142001

RECEIVED

11 MAR 2004

WIPO

PCT

# THE UNITED STATES OF AMERICA

**TO ALL TO WHOM THESE PRESENTS SHALL COME;**

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office

March 09, 2004

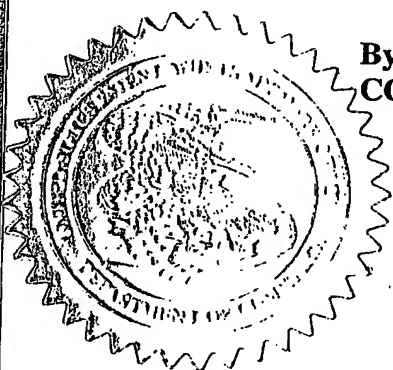
THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: 60/437,377

FILING DATE: January 02, 2003

RELATED PCT APPLICATION NUMBER: PCT/US03/41745

By Authority of the  
COMMISSIONER OF PATENTS AND TRADEMARKS



*M. Sias*  
M. SIAS  
Certifying Officer

**PRIORITY DOCUMENT**  
SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH  
RULE 17.1(a) OR (b)

01-02-0343333-11-12 APPROV  
SH11/02/03  
31331 U.S. PTOPTO/SB/16 (10-01)  
Approved for use through 10/31/2002. OMB 0651-0036  
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE  
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.**PROVISIONAL APPLICATION FOR PATENT COVER SHEET**

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 064 965 626 US

INVENTOR(S)					
Given Name (first and middle [if any])		Family Name or Surname		Residence (City and either State or Foreign Country)	
Gerard M.		Housey		28520 Streamwood Lane; Southfield, MI 48034	
Morris F.		White		14 Gretter Road; West Roxbury, MA 02131-1315	
<input type="checkbox"/> Additional inventors are being named on the _____ Separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
IRS MODULATORS					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
<input checked="" type="checkbox"/> Customer Number		010291		<input type="checkbox"/>	
OR		Customer Number		Customer Number Bar Code	
<input checked="" type="checkbox"/> Firm or Individual Name		Christopher J. Voci, Esq.			
Address		Rader, Fishman & Grauer PLLC 39533 Woodward Avenue, Ste. 140			
City		Bloomfield Hills		State	Michigan
Country		USA		Zip	48304
		Telephone	248-594-0600		Fax
		248-594-0610			
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification Number of Pages		15		<input type="checkbox"/> CD(s), Number	
<input type="checkbox"/> Drawing(s) Number of Sheets				<input type="checkbox"/> Other:	
<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76					
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.				FILING FEE AMOUNT (\$)	
<input type="checkbox"/> A check or money order is enclosed to cover the filing fees					
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:		18-0013		\$80.00	
<input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.					
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
<input checked="" type="checkbox"/> No		<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are:			

Respectfully submitted,

SIGNATURE



Date December 31, 2002

TYPED OR

PRINTED NAME

Christopher J. Voci

REGISTRATION NO.  
(if appropriate)

45,184

TELEPHONE

248-594-0648

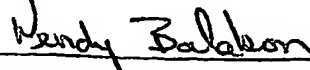
Docket Number:

12000-0002

**USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT**Provisional Application for Patent  
I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV 064965626 US, in an envelope addressed to: Box Provisional Patent Application, Commissioner for Patents, Washington, DC 20231, on the date shown below.

Dated: December 31, 2002

Signature:



(Wendy A. Balaban)

<h2 style="margin: 0;">FEE TRANSMITTAL</h2> <h3 style="margin: 0;">for FY 2002</h3> <p style="margin: 0; font-size: small;">Patent fees are subject to annual revision.</p>		<p><b>Complete if Known</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Application Number</td> <td style="width: 50%;">To Be Assigned</td> </tr> <tr> <td>Filing Date</td> <td>Herewith</td> </tr> <tr> <td>First Named Inventor</td> <td>Gerard M. Housey, et al.</td> </tr> <tr> <td>Examiner Name</td> <td></td> </tr> <tr> <td>Group Art Unit</td> <td>Unknown</td> </tr> <tr> <td>Attorney Docket No.</td> <td>66112-999</td> </tr> </table>		Application Number	To Be Assigned	Filing Date	Herewith	First Named Inventor	Gerard M. Housey, et al.	Examiner Name		Group Art Unit	Unknown	Attorney Docket No.	66112-999
Application Number	To Be Assigned														
Filing Date	Herewith														
First Named Inventor	Gerard M. Housey, et al.														
Examiner Name															
Group Art Unit	Unknown														
Attorney Docket No.	66112-999														
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27															
<b>TOTAL AMOUNT OF PAYMENT</b> (\$) <b>80.00</b>															

<p><b>METHOD OF PAYMENT</b> (check all that apply)</p> <p> <input type="checkbox"/> Check             <input type="checkbox"/> Credit Card             <input type="checkbox"/> Money Order             <input type="checkbox"/> Other             <input type="checkbox"/> None         </p> <p><input checked="" type="checkbox"/> Deposit Account</p> <p>Deposit Account Number: <span style="border: 1px solid black; padding: 2px;">010291</span></p> <p>Deposit Account Name: <span style="border: 1px solid black; padding: 2px;">Rader, Fishman &amp; Grauer PLLC</span></p> <p>The Commissioner is hereby authorized to: (check all that apply)</p> <p> <input checked="" type="checkbox"/> Charge fee(s) indicated below             <input checked="" type="checkbox"/> Credit any overpayments         </p> <p> <input checked="" type="checkbox"/> Charge any additional fee(s) during the pendency of this application         </p> <p> <input type="checkbox"/> Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.         </p>				<p><b>FEE CALCULATION</b> (continued)</p>																																																																																																																																																																																																																																															
<p><b>1. BASIC FILING FEE</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2">Large Entity</th> <th colspan="2">Small Entity</th> <th rowspan="2">Fee Description</th> <th rowspan="2">Fee Paid</th> </tr> <tr> <th>Fee Code</th> <th>Fee (\$)</th> <th>Fee Code</th> <th>Fee (\$)</th> </tr> </thead> <tbody> <tr> <td>1001</td> <td>740</td> <td>2001</td> <td>370</td> <td>Utility filing fee</td> <td></td> </tr> <tr> <td>1002</td> <td>330</td> <td>2002</td> <td>165</td> <td>Design filing fee</td> <td></td> </tr> <tr> <td>1003</td> <td>510</td> <td>2003</td> <td>255</td> <td>Plant filing fee</td> <td></td> </tr> <tr> <td>1004</td> <td>740</td> <td>2004</td> <td>370</td> <td>Reissue filing fee</td> <td></td> </tr> <tr> <td>1005</td> <td>160</td> <td>2005</td> <td>80</td> <td>Provisional filing fee</td> <td>80</td> </tr> <tr> <td colspan="5" style="text-align: right;"><b>SUBTOTAL (1)</b></td> <td>(\$80)</td> </tr> </tbody> </table>				Large Entity		Small Entity		Fee Description	Fee Paid	Fee Code	Fee (\$)	Fee Code	Fee (\$)	1001	740	2001	370	Utility filing fee		1002	330	2002	165	Design filing fee		1003	510	2003	255	Plant filing fee		1004	740	2004	370	Reissue filing fee		1005	160	2005	80	Provisional filing fee	80	<b>SUBTOTAL (1)</b>					(\$80)	<p><b>3. ADDITIONAL FEES</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2">Large Entity</th> <th colspan="2">Small Entity</th> <th rowspan="2">Fee Description</th> <th rowspan="2">Fee Paid</th> </tr> <tr> <th>Fee Code</th> <th>Fee (\$)</th> <th>Fee Code</th> <th>Fee (\$)</th> </tr> </thead> <tbody> <tr> <td>1051</td> <td>130</td> <td>2051</td> <td>65</td> <td>Surcharge - late filing fee or oath</td> <td></td> </tr> <tr> <td>1052</td> <td>50</td> <td>2052</td> <td>25</td> <td>Surcharge - late provisional filing fee or cover sheet</td> <td></td> </tr> <tr> <td>1053</td> <td>130</td> <td>1053</td> <td>130</td> <td>Non-English specification</td> <td></td> </tr> <tr> <td>1812</td> <td>2,520</td> <td>1812</td> <td>2,520</td> <td>For filing a request for <i>ex parte</i> reexamination</td> <td></td> </tr> <tr> <td>1804</td> <td>920*</td> <td>1804</td> <td>920*</td> <td>Requesting publication of SIR prior to Examiner action</td> <td></td> </tr> <tr> <td>1805</td> <td>1,840*</td> <td>1805</td> <td>1,840*</td> <td>Requesting publication of SIR after Examiner action</td> <td></td> </tr> <tr> <td>1251</td> <td>110</td> <td>2251</td> <td>55</td> <td>Extension for reply within first month</td> <td></td> </tr> <tr> <td>1252</td> <td>400</td> <td>2252</td> <td>200</td> <td>Extension for reply within second month</td> <td></td> </tr> <tr> <td>1253</td> <td>920</td> <td>2253</td> <td>460</td> <td>Extension for reply within third month</td> <td></td> </tr> <tr> <td>1254</td> <td>1,440</td> <td>2254</td> <td>720</td> <td>Extension for reply within fourth month</td> <td></td> </tr> <tr> <td>1255</td> <td>1,960</td> <td>2255</td> <td>980</td> <td>Extension for reply within fifth month</td> <td></td> </tr> <tr> <td>1401</td> <td>320</td> <td>2401</td> <td>160</td> <td>Notice of Appeal</td> <td></td> </tr> <tr> <td>1402</td> <td>320</td> <td>2402</td> <td>160</td> <td>Filing a brief in support of an appeal</td> <td></td> </tr> <tr> <td>1403</td> <td>280</td> <td>2403</td> <td>140</td> <td>Request for oral hearing</td> <td></td> </tr> <tr> <td>1451</td> <td>1,510</td> <td>1451</td> <td>1,510</td> <td>Petition to institute a public use proceeding</td> <td></td> </tr> <tr> <td>1452</td> <td>110</td> <td>2452</td> <td>55</td> <td>Petition to revive - unavoidable</td> <td></td> </tr> <tr> <td>1453</td> <td>1,280</td> <td>2453</td> <td>640</td> <td>Petition to revive - unintentional</td> <td></td> </tr> <tr> <td>1501</td> <td>1,280</td> <td>2501</td> <td>640</td> <td>Utility issue fee (or reissue)</td> <td></td> </tr> <tr> <td>1502</td> <td>460</td> <td>2502</td> <td>230</td> <td>Design issue fee</td> <td></td> </tr> <tr> <td>1503</td> <td>620</td> <td>2503</td> <td>310</td> <td>Plant issue fee</td> <td></td> </tr> <tr> <td>1460</td> <td>130</td> <td>1460</td> <td>130</td> <td>Petitions to the Commissioner</td> <td></td> </tr> <tr> <td>1807</td> <td>50</td> <td>1807</td> <td>50</td> <td>Processing fee under 37 CFR 1.17(q)</td> <td></td> </tr> <tr> <td>1808</td> <td>180</td> <td>1808</td> <td>180</td> <td>Submission of Information Disclosure Stmt</td> <td></td> </tr> <tr> <td>8021</td> <td>40</td> <td>8021</td> <td>40</td> <td>Recording each patent assignment per property (times number of properties)</td> <td></td> </tr> <tr> <td>1809</td> <td>740</td> <td>2809</td> <td>370</td> <td>Filing a submission after final rejection (37 CFR 1.129(a))</td> <td></td> </tr> <tr> <td>1810</td> <td>740</td> <td>2810</td> <td>370</td> <td>For each additional invention to be examined (37CFR 1.129(b))</td> <td></td> </tr> <tr> <td>1801</td> <td>740</td> <td>2801</td> <td>370</td> <td>Request for Continued Examination (RCE)</td> <td></td> </tr> <tr> <td>1802</td> <td>900</td> <td>1802</td> <td>900</td> <td>Request for expedited examination of a design application</td> <td></td> </tr> <tr> <td colspan="5">Other fee (specify)</td> <td></td> </tr> <tr> <td colspan="5" style="text-align: right;"><b>SUBTOTAL (3)</b></td> <td>(\$)</td> </tr> </tbody> </table>				Large Entity		Small Entity		Fee Description	Fee Paid	Fee Code	Fee (\$)	Fee Code	Fee (\$)	1051	130	2051	65	Surcharge - late filing fee or oath		1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet		1053	130	1053	130	Non-English specification		1812	2,520	1812	2,520	For filing a request for <i>ex parte</i> reexamination		1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action		1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action		1251	110	2251	55	Extension for reply within first month		1252	400	2252	200	Extension for reply within second month		1253	920	2253	460	Extension for reply within third month		1254	1,440	2254	720	Extension for reply within fourth month		1255	1,960	2255	980	Extension for reply within fifth month		1401	320	2401	160	Notice of Appeal		1402	320	2402	160	Filing a brief in support of an appeal		1403	280	2403	140	Request for oral hearing		1451	1,510	1451	1,510	Petition to institute a public use proceeding		1452	110	2452	55	Petition to revive - unavoidable		1453	1,280	2453	640	Petition to revive - unintentional		1501	1,280	2501	640	Utility issue fee (or reissue)		1502	460	2502	230	Design issue fee		1503	620	2503	310	Plant issue fee		1460	130	1460	130	Petitions to the Commissioner		1807	50	1807	50	Processing fee under 37 CFR 1.17(q)		1808	180	1808	180	Submission of Information Disclosure Stmt		8021	40	8021	40	Recording each patent assignment per property (times number of properties)		1809	740	2809	370	Filing a submission after final rejection (37 CFR 1.129(a))		1810	740	2810	370	For each additional invention to be examined (37CFR 1.129(b))		1801	740	2801	370	Request for Continued Examination (RCE)		1802	900	1802	900	Request for expedited examination of a design application		Other fee (specify)						<b>SUBTOTAL (3)</b>					(\$)
Large Entity		Small Entity		Fee Description	Fee Paid																																																																																																																																																																																																																																														
Fee Code	Fee (\$)	Fee Code	Fee (\$)																																																																																																																																																																																																																																																
1001	740	2001	370	Utility filing fee																																																																																																																																																																																																																																															
1002	330	2002	165	Design filing fee																																																																																																																																																																																																																																															
1003	510	2003	255	Plant filing fee																																																																																																																																																																																																																																															
1004	740	2004	370	Reissue filing fee																																																																																																																																																																																																																																															
1005	160	2005	80	Provisional filing fee	80																																																																																																																																																																																																																																														
<b>SUBTOTAL (1)</b>					(\$80)																																																																																																																																																																																																																																														
Large Entity		Small Entity		Fee Description	Fee Paid																																																																																																																																																																																																																																														
Fee Code	Fee (\$)	Fee Code	Fee (\$)																																																																																																																																																																																																																																																
1051	130	2051	65	Surcharge - late filing fee or oath																																																																																																																																																																																																																																															
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet																																																																																																																																																																																																																																															
1053	130	1053	130	Non-English specification																																																																																																																																																																																																																																															
1812	2,520	1812	2,520	For filing a request for <i>ex parte</i> reexamination																																																																																																																																																																																																																																															
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action																																																																																																																																																																																																																																															
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action																																																																																																																																																																																																																																															
1251	110	2251	55	Extension for reply within first month																																																																																																																																																																																																																																															
1252	400	2252	200	Extension for reply within second month																																																																																																																																																																																																																																															
1253	920	2253	460	Extension for reply within third month																																																																																																																																																																																																																																															
1254	1,440	2254	720	Extension for reply within fourth month																																																																																																																																																																																																																																															
1255	1,960	2255	980	Extension for reply within fifth month																																																																																																																																																																																																																																															
1401	320	2401	160	Notice of Appeal																																																																																																																																																																																																																																															
1402	320	2402	160	Filing a brief in support of an appeal																																																																																																																																																																																																																																															
1403	280	2403	140	Request for oral hearing																																																																																																																																																																																																																																															
1451	1,510	1451	1,510	Petition to institute a public use proceeding																																																																																																																																																																																																																																															
1452	110	2452	55	Petition to revive - unavoidable																																																																																																																																																																																																																																															
1453	1,280	2453	640	Petition to revive - unintentional																																																																																																																																																																																																																																															
1501	1,280	2501	640	Utility issue fee (or reissue)																																																																																																																																																																																																																																															
1502	460	2502	230	Design issue fee																																																																																																																																																																																																																																															
1503	620	2503	310	Plant issue fee																																																																																																																																																																																																																																															
1460	130	1460	130	Petitions to the Commissioner																																																																																																																																																																																																																																															
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)																																																																																																																																																																																																																																															
1808	180	1808	180	Submission of Information Disclosure Stmt																																																																																																																																																																																																																																															
8021	40	8021	40	Recording each patent assignment per property (times number of properties)																																																																																																																																																																																																																																															
1809	740	2809	370	Filing a submission after final rejection (37 CFR 1.129(a))																																																																																																																																																																																																																																															
1810	740	2810	370	For each additional invention to be examined (37CFR 1.129(b))																																																																																																																																																																																																																																															
1801	740	2801	370	Request for Continued Examination (RCE)																																																																																																																																																																																																																																															
1802	900	1802	900	Request for expedited examination of a design application																																																																																																																																																																																																																																															
Other fee (specify)																																																																																																																																																																																																																																																			
<b>SUBTOTAL (3)</b>					(\$)																																																																																																																																																																																																																																														
<p><b>2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE</b></p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th colspan="2">Large Entity</th> <th colspan="2">Small Entity</th> <th rowspan="2">Fee Description</th> <th rowspan="2">Fee Paid</th> </tr> <tr> <th>Fee Code</th> <th>Fee (\$)</th> <th>Fee Code</th> <th>Fee (\$)</th> </tr> </thead> <tbody> <tr> <td>1202</td> <td>18</td> <td>2202</td> <td>9</td> <td>Claims in excess of 20</td> <td></td> </tr> <tr> <td>1201</td> <td>84</td> <td>2201</td> <td>42</td> <td>Independent claims in excess of 3</td> <td></td> </tr> <tr> <td>1203</td> <td>280</td> <td>2203</td> <td>140</td> <td>Multiple dependent claim, if not paid</td> <td></td> </tr> <tr> <td>1204</td> <td>84</td> <td>2204</td> <td>42</td> <td>** Reissue independent claims over original patent</td> <td></td> </tr> <tr> <td>1205</td> <td>18</td> <td>2205</td> <td>9</td> <td>** Reissue claims in excess of 20 and over original patent</td> <td></td> </tr> <tr> <td colspan="5" style="text-align: right;"><b>SUBTOTAL (2)</b></td> <td>(\$)</td> </tr> </tbody> </table> <p><small>**or number previously paid, if greater; For Reissues, see above</small></p>				Large Entity		Small Entity		Fee Description	Fee Paid	Fee Code	Fee (\$)	Fee Code	Fee (\$)	1202	18	2202	9	Claims in excess of 20		1201	84	2201	42	Independent claims in excess of 3		1203	280	2203	140	Multiple dependent claim, if not paid		1204	84	2204	42	** Reissue independent claims over original patent		1205	18	2205	9	** Reissue claims in excess of 20 and over original patent		<b>SUBTOTAL (2)</b>					(\$)	<p><b>Reduced by Basic Filing Fee Paid</b></p> <p><b>SUBTOTAL (3)</b> (\$)</p>																																																																																																																																																																																																	
Large Entity		Small Entity		Fee Description	Fee Paid																																																																																																																																																																																																																																														
Fee Code	Fee (\$)	Fee Code	Fee (\$)																																																																																																																																																																																																																																																
1202	18	2202	9	Claims in excess of 20																																																																																																																																																																																																																																															
1201	84	2201	42	Independent claims in excess of 3																																																																																																																																																																																																																																															
1203	280	2203	140	Multiple dependent claim, if not paid																																																																																																																																																																																																																																															
1204	84	2204	42	** Reissue independent claims over original patent																																																																																																																																																																																																																																															
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent																																																																																																																																																																																																																																															
<b>SUBTOTAL (2)</b>					(\$)																																																																																																																																																																																																																																														

<p><b>SUBMITTED BY</b></p>				<p><b>Complete (if applicable)</b></p>					
Name (Print/Type)	Christopher J. Voci			Registration No. (Attorney/Agent)	45,184		Telephone	248-594-0648	
Signature				Date	December 31, 2002				

**Express Mail Label No. EV 064 965 626US**

**UNITED STATES PATENT AND TRADEMARK OFFICE**

**Patent Application for an invention entitled**

**IRS MODULATORS**

**By:**

**Dr. Gerard M. Housey  
a U.S. citizen, residing at  
28520 Streamwood Lane  
Southfield, Michigan 48034**

**and**

**Dr. Morris F. White  
a U.S. citizen, residing at  
14 Gretter Road  
West Roxbury, MA 02131-1315**

**Prepared by:**

**James F. Kamp, Esq.; Registration No.: 41,882  
Christopher J. Voci, Esq.; Registration No. 45,184  
Attorney Docket No.: 66112-999  
Customer No.: 010291  
Rader Fishman & Grauer, PLLC  
39533 Woodward Avenue, Suite 140  
Bloomfield Hills, Michigan 48304  
(248) 594-0600**

Attorney Docket No. 66112-999

EV 064 965 626 US

**IRS MODULATORS****Field of the Invention**

This is a general method for the prevention, induction of long term remission, or even the cure of various metabolic disorders in human beings and animals, including type II diabetes, by regulating the Irs2/Irs1 ratio in cells and tissues in the body. Irs1 and Irs2 are part of the insulin or insulin like growth factor signaling pathways, but also mediate signals by other growth factors and cytokines, including IFN $\gamma$ , IL2, IL4, IL7, IL9, IL13 or IL15; growth hormone, prolactin, or leptin. Irs1 or Irs2 functional activity also integrates signals emanating from proinflammatory cytokines, including TNF $\alpha$ , IL6, IL1 $\beta$  and related factors. In general proinflammatory cytokines inhibit Irs1/Irs2 signaling which might contribute to insulin resistance syndromes.

Experiments in transgenic mice reveal that the essential role of Irs1 and Irs2 is to promote somatic growth and nutrient homeostasis. Without Irs1, mice are 50% smaller than normal from birth until they die at 2 years of age. Insulin secretion from pancreatic  $\beta$ -cells might be impaired in mice lacking Irs1. Mice without Irs1 have less body fat. Mice without Irs1 are glucose intolerant. People with type 2 diabetes display reduced Irs1 signaling in various peripheral tissues, especially in muscle and fat.

Experiments in transgenic mice reveal the essential role for Irs2 is in peripheral insulin action and the function, growth and survival of pancreatic  $\beta$ -cells. In mice, Irs2 is important for peripheral insulin action, as mice lacking Irs2 display glucose intolerance and hyperlipidemia. Pancreatic  $\beta$ -cells of mice lacking Irs2 fail to survive and secrete sufficient insulin to compensate for the peripheral insulin resistance, which results in diabetes. By upregulating the levels or enhancing the cellular functional activity of Irs2 relative to Irs1, insulin is used more efficiently by the body to control nutrient levels. By upregulating the levels or enhancing the cellular functional activity of Irs2 relative to Irs1 in pancreatic  $\beta$ -cells, glucose sensing and insulin secretion is improved. Thus, methods to upregulate or enhance the functional cellular activity of Irs2 relative to Irs1 will promote insulin secretion and insulin action and prevent diabetes and related metabolic disorders.

Attorney Docket No. 66112-999

EV 064 965 626 US

People with type 2 diabetes display reduced levels of Irs2 activity in various tissues accessible to testing, including muscle or fat.

Irs2 promotes brain growth during mouse development. Irs2 is important for 50% of brain growth. Moreover, without Irs2, phosphorylated Tau, a marker for Alzheimer disease accumulates in the hippocampus of mice. So, upregulation of Irs2 or increased function of Irs2 may prevent, reverse or cure neurological degenerative disease like Alzheimer's.

Irs2 promotes growth of the retina. Mice lacking Irs2 display increased loss of retinal neurons, especially rod and cones. This leads to blindness. Upregulation of Irs2 or increased Irs2 activity might prevent retinal degeneration or promote retinal growth and regeneration.

#### Abstract of the Invention

This invention is directed to a general method for the chronic treatment, potential cure, or prevention of various metabolic and related disorders in people, including diabetes, by regulating the Irs2/Irs1 ratio in cells and tissues in the body. Irs1 and Irs2 are part of the insulin/IGF1 signaling pathway. Experiments in transgenic mice reveal an essential role for Irs2 in peripheral insulin action and the function, growth and survival of pancreatic  $\beta$ -cells. By upregulating the levels or functional activity of Irs2 relative to Irs1, insulin is used more efficiently by the body to control nutrient levels. By upregulating Irs2 levels or functional activity relative to Irs1 in pancreatic  $\beta$ -cells, glucose sensing and insulin secretion are enhanced. Thus methods to upregulate levels or functional activity of Irs2 relative to Irs1 will promote insulin secretion and insulin action and prevent diabetes and related metabolic disorders. This invention has been tested in mice.

#### Background of the Invention

**Definition:** Compounds which inhibit a protein (inhibitors or antagonists), activate a protein (activators or agonists), or stabilize the interaction between Irs2 and another binding

Attorney Docket No. 66112-999

EV 064 965 626 US

protein, all exert their effects by interacting with (binding to) Irs2 or to a protein complex (such as a heterodimer) one component of which is comprised of Irs2.

Diabetes is a life threatening disease that has been known for more than 2000 years. It occurs in mammals as diverse as monkeys, dogs, rats, mice and human beings. The discovery of insulin and its purification in 1921 for use in people provided a partial treatment for diabetes that is still in widespread use today. Insulin levels are ordinarily adjusted by the body on a moment to moment basis to keep the blood sugar level within a narrow physiological range. Periodic insulin injections, however, can only approximate the normal state because the cellular response to insulin in many cases is also reduced. Consequently, for these and other reasons which will be discussed in detail below, life threatening complications still occur during the lifetime of treated diabetic patients, especially in the case of type II (adult-onset) diabetes.

This invention describes a set of methods to upregulate the level or functional activity of Irs2 in human beings and other mammals which will ameliorate or even prevent the failure or massive destruction of pancreatic  $\beta$ -cells that causes certain forms of diabetes, and reduce the need for insulin by peripheral insulin sensitive tissues. Background information which provided a foundation for this invention was the discovery of a family of target proteins that function immediately downstream of the insulin receptor or insulin like growth factor receptors in mediating cellular functions. This target protein family, now termed the insulin receptor substrate (Irs) protein family, has been shown in subsequent studies, to be of central importance in mediating the effects of insulin on responsive cells.

The Insulin Receptor Substrate 2 (Irs2) is a signaling scaffold protein that ordinarily exists in all cells of the body. In liver, muscle, fat, brain and other peripheral tissues it mediates the effects of insulin, insulin-like growth factors, or other cytokines upon cellular metabolism, growth, and survival by regulating the activity of numerous enzymes and genes. It also has effects in pancreatic  $\beta$ -cells where it strongly promotes growth, function and survival. By upregulating Irs2 function or expression in  $\beta$ -cells diabetes can be prevented because existing

$\beta$ -cells may be maintained in a functional state, thereby able to sense glucose levels and secrete sufficient insulin.

The first member of the insulin receptor substrate family of proteins was discovered in 1985, and subsequent research efforts revealed the existence of related Irs family members as well as the signaling pathways to which the Irs proteins are linked. After the discovery that the Insulin Receptor (IR) possessed a tyrosine kinase enzyme activity, many groups searched for insulin receptor substrates that might regulate downstream signaling from the receptor. The first evidence for the existence of an actual target protein for the Insulin Receptor, subsequently named an Insulin Receptor Substrate, or "Irs" protein, resulted from the use of phosphotyrosine antibody immunoprecipitates which surprisingly revealed a 185-kDa phosphoprotein (pp185) in insulin-stimulated hepatoma cells. Purification and molecular cloning of pp185 revealed one of the first signaling scaffolds as well as the first Insulin Receptor Substrate protein (Irs1). U.S. Patent No. 5,260,200. Irs1 was determined to be biologically important because it was phosphorylated immediately after insulin stimulation, and catalytically active insulin receptor mutants that failed to phosphorylate Irs1 were biologically inactive.

Irs1 contains many tyrosine phosphorylation sites that are phosphorylated during insulin and insulin-like growth factor 1 (IGF1) stimulation, and bind to the Src homology-2 domains in various signaling proteins. The interaction between Irs1 and p85 activates the class 1A phosphatidylinositol 3-kinase, thereby revealing the first insulin signaling cascade that could be reconstituted successfully in cells and test tubes.

Several experiments suggested that other related proteins might exist: Irs1 antibodies did not react completely with the phosphotyrosine containing protein that migrated at 185 kDa during SDS-PAGE; FDCP1 cells contained a protein with characteristics similar to those of Irs1 but failed to completely to react with antibodies directed against Irs1; the liver of transgenic mice lacking Irs1 still contained a protein in liver that had characteristics of Irs1. All of these finding led one of the Applicants' to pursue the purification and cloning of a second member of the Irs family, Irs2. U.S. Patent No. 5,858,701.



Attorney Docket No. 66112-999

EV 064 965 626 US

Disruption of the *Irs2* gene in mice using standard gene knockout approaches results in diabetes that develops during the first 10 to 12 weeks of age. Pancreatic  $\beta$ -cells are lost from these mice as they age. Moreover, genes that are important for  $\beta$ -cell function are down regulated in mice lacking *Irs2*. Most importantly, transgenic replacement of *Irs2* in  $\beta$ -cells restores their function and cures diabetes in various mouse model systems.

From the integration of these and other experimental systems in mice, taken together with *in vitro* results obtained from intact cellular systems as well as subsequent unpublished observations, it became apparent to Applicants' that upregulation of the level or functional activity of *Irs2* in humans will result in a therapeutically effective chronic treatment for patients suffering from diabetes, especially the adult onset (type II) form of the disease, as well as for other disorders in which *Irs* protein function is insufficient, abnormal or absent altogether.

#### Summary of the invention

This invention pertains to generalized methods of preventing, curing or inducing durable long-term remissions in patients with diabetes, metabolic disorders, central nervous system diseases, obesity, fertility and other human disorders in which an inappropriate level of functional cellular activity of the *Irs* family of proteins contribute to the disease state. The invention is particularly concerned with the modulation of the activity of *Irs2*-mediated cellular signaling pathways as a mechanism for treating human disease.

There are two important elements of the invention disclosed herein which may be described as follows. The first element involves the key concept of enhancing (i.e. stabilizing) the *Irs2* binding interaction with various proteins both upstream and downstream that interact with (bind to) *Irs2*. These include, for example, the human Insulin Receptor (HIR) which binds to and phosphorylates *Irs2*, the N-terminal c-jun kinase (JNK), as well additional upstream or downstream signaling elements such as src homology 2 (SH2) domain-containing proteins that bind to *Irs2* and may also phosphorylate or otherwise modify *Irs2* as well. The second important element involves the specific pattern of covalent modifications of *Irs2* such as

phosphorylation of serine, threonine and tyrosine residues, ubiquitination patterns, or other covalent modification that alter the function, intracellular localization, or stability of Irs2.

Although certain of these effects may be opposite in nature depending upon the cellular context, such modulations may be achieved pharmacologically with compounds, (and especially small molecules), that either stabilize Irs2 interactions with other proteins or accelerate the "off" rate of such interactions after Irs2 has interacted with said proteins. Depending upon the cellular context, any of the aforementioned activities will lead to alterations in cellular functioning of the Irs2-mediated signal transduction cascades, resulting in improvements in cellular signaling relevant to the disease states of interest as will be discussed in detail below.

The method involves upregulating the expression or functional cellular activity of Irs2 relative to Irs1 or other Irs family members or other proteins. Upregulation of the Irs2 gene or Irs2 protein function promotes cell and tissue functions particular to the specific target tissue. Methods that promote Irs2 signaling, by upregulating Irs2 expression or Irs2 function in specific tissues can target or prevent specific diseases involving those specific tissues or cells. For example, upregulation of Irs2 in pancreatic  $\beta$ -cells improves glucose stimulated insulin secretion. Drugs that upregulate the Irs2 gene or promote Irs2 signaling in  $\beta$ -cells will promote  $\beta$ -cell function and prevent or cure diabetes; upregulation of Irs2 in the hippocampus can reduce phosphorylated Tau, a marker of Alzheimer's disease and prevents onset of the disease. Upregulation of Irs2 in hypothalamus promotes expression and release of neuropeptides that control appetite and may promote weight loss. Irs2 is also important in peripheral tissues that respond to insulin, so upregulation of the Irs2 gene or upregulation of Irs2 signaling function makes tissues more sensitive to insulin and thus less insulin is needed to elicit the appropriate response. In one embodiment, two or more different drugs may be used to promote Irs2 gene expression or Irs2 function in  $\beta$ -cells or in hepatocytes or in neurons. Alternatively, a single compound might promote Irs2 gene expression or Irs2 signaling and function in all of these tissues. These effects of Irs2 work together to keep glucose under control and prevent diabetes and related disorders that are modulated by Irs2 function.

**Attorney Docket No. 66112-999**

**EV 064 965 626 US**

The inventions further comprise methods to discover and utilize compounds that upregulate the function or levels of Irs2 in people to prevent or cure disease associated with insulin resistance syndrome, especially diabetes.

The invention can also be used to determine whether known drugs already in use for the treatment of other diseases also promote Irs2 signaling functions or upregulation of Irs2 gene expression. This would reveal new mechanisms of action for old drugs that might indicate their use in human diseases caused by failure of the Irs2 signaling system, such as insulin resistance, diabetes and the complications resulting from these disorders.

In another example, upregulation of Irs2 expression or an increase of Irs2 signaling function can also be beneficial to other tissues. For example, approximately half of the growth of a mouse brain depends on the expression of the Irs2 gene. Therefore, drugs that promote Irs2 signaling will also be expected to promote brain growth in mammals and people. Irs2 signaling also plays a role in dephosphorylation of the Tau protein, a marker of Alzheimer disease. Upregulation of Irs2 in the hippocampus should promote normal function and contribute to the prevention of the neuronal degeneration associated with Alzheimer disease.

Irs2 signaling also plays a role in feeding behavior and female fertility. Mice lacking Irs2 tend to gain weight as a result of the inability of the brain to properly assess whether insulin has been secreted or not after a meal, so the brain can not determine whether a meal has in fact been consumed. Upregulation of Irs2 in the hypothalamus, and more specifically which may include the arcuate nucleus of the hypothalamus, will promote appetite regulation that results in reduced weight gain or even weight loss.

#### **Examples of the Uses of Various Aspects of the Invention**

##### **Assay systems for identification and subsequent use of modulators of Irs2 function.**

Cell-based assay systems capable of being adapted specifically for the examples which follow below have been previously developed by Applicants (See, for example, US 5,688,655).

Furthermore, certain cell-free assay systems are also useful for use in identifying compounds as discussed in detail in the examples given below. One such cell-free system consists of an

**Attorney Docket No. 66112-999**

**EV 064 965 626 US**

electrochemiluminescence methodology whereby protein-protein interactions may be measured by the emission of light at a specific wavelength when the IR interacts with (i.e binds to) Irs2. Such cell free assay systems are also capable of being utilized in the identification and characterization of compounds as discussed in detail in the examples given below. Other examples are well known to investigators of skill in the art.

**Methods of identifying and using compounds that inhibit the degradation of Irs2 in  $\beta$ -cells.**

In the most general approach, cell-based screens can be established to identify compounds that block the intracellular degradation of Irs2. Although a variety of cell types can be used for this process, one that expresses (or overexpresses) Irs2 would be preferable, for example, according to prior teachings of U.S. 5,688,655 and related patents. Also, engineering an Irs2 cDNA for the purpose of detecting degradation of Irs2 would also be useful. This may be performed, for example, through the addition of a flag tag at the COOH end of the molecule. More detailed information is also available to accomplish this goal. For example, ubiquitination promotes degradation of both Irs1 and Irs2. Therefore, certain drugs that inhibit ubiquitination would be anticipated to protect cells from the deleterious effects that result from the loss of Irs2. Such drugs can also be identified using cell-based screens.

**Methods of identifying and using compounds that upregulate Irs2 function in  $\beta$ -cells.**

Another way to upregulate Irs2 expression is to find a drug that stimulates transcription of the Irs2 genes. This can also be performed with the cell based screening methods described above. Beta-cell lines, such as Min6 cells may be prepared with an artificial Irs2 gene that contains an easily detectable readout such as a green fluorescence protein (GFP) to facilitate high throughput screening. PCR based screening methods may also be used to directly detect the expression of the endogenous gene. The hits can be tested for function on isolated mouse or human islet cells. Tissue specificity of the hits can be tested across various cell lines to determine whether the identified compounds are specific for  $\beta$ -cells or also promote Irs2 expression in other cells.

**Methods of using glucagon like peptide 1 (GLP-1) to upregulate Irs2 in beta cells and other tissues.**

GLP-1, as well as stable analogs like Exendin-4, has been suggested as potential treatments for diabetes because they appear to promote insulin secretion in response to increases in plasma glucose levels. GLP-1 has been shown to reverse the age-dependent decline in  $\beta$ -cell function in rats or mice. Furthermore, GLP-1 also stimulates  $\beta$ -cell proliferation and neogenesis, and reduces or eliminates apoptosis of  $\beta$ -cells. In addition, GLP-1 secretion has also been shown to decrease in people with Type II diabetes, however subcutaneous administration of GLP-1 is able to improve glucose homeostasis; lower body weight, reduce circulating plasma free fatty acid and hemoglobin A(1C) and increase cellular responsiveness to insulin. Interestingly, attempts to restore normal glucose homeostasis in  $Irs2^{-/-}$  mice by the administration of Exendin-4 by injection were unsuccessful, demonstrating that Irs2 plays an important role.

**Compounds and methods of using GLP-1 analogs that upregulate Irs2 in beta cells.**

Since GLP-1 promotes expression of Irs2, small molecules (i.e. chemical agents with molecular weights less than or equal to 1,000 atomic mass units (Daltons) that are chemical analogues will also be able to increase Irs2 expression. Such chemical compounds will preferably be orally available and can be used to promote Irs2 expression in  $\beta$ -cells and other cells that contain GLP-1 receptors.

**Compounds and methods of using cyclic AMP modulators to upregulate Irs2 in beta cells and other tissues.**

Drugs that upregulate the concentration of cAMP in cells are well known. Since Irs2 expression is modulated in part by cAMP levels in some cells, many current drugs may exert some of their effects by functioning through the upregulation of Irs2. Thus, evaluating known drugs for specific effects on Irs2 expression in tissues will reveal new uses of the known drugs for the treatment of disease related to the loss of Irs2 expression or cellular function. Some of the effects of certain known drugs may be dependent upon their ability to upregulate Irs2.

**Compounds and methods of identifying and using tissue-specific agonists that upregulate Irs2 in tissues of the body to prevent diseases of insulin resistance syndrome.**

One kind of drug that upregulates Irs2 might work on all tissues of the body, another kind of compound might display tissue specific specificity. This invention provides a way to assess the effect(s) of known and unknown drugs on the tissue-specific expression of Irs2. As known to one of skill in this art, one method to do this is to construct a mouse that contains an Irs2 construct containing a carboxyterminal (COOH) extension comprised of the green fluorescent protein. After administration of compounds to the test animal, all tissues can be evaluated for expression of the tagged Irs2 protein to establish the tissue-specific effects of the particular compound with respect to the expression of the Irs2 gene.

**Methods of identifying and using compounds that stimulate signaling by Irs2 in  $\beta$ -cells and other cell types.**

Irs2 signaling is inhibited by many pathways including degradation and serine phosphorylation. Compounds that inhibit these processes will upregulate Irs2 function. As discussed previously, a general cell based assay system can be set up to identify compounds that increase Irs2 signaling. Various readouts may be used to determine when such drugs are identified, including glucose uptake by the cell or the subsequent expression of other known downstream genes. For example, specific serine phosphorylation sites are known to inhibit Irs2 function. Compounds that inhibit phosphorylation of these inhibitor serine residues can be identified and these used to protect Irs2 function and prevent diabetes, the complications of diabetes or the insulin resistance syndrome, or other disorders in which Irs2 function plays a role as discussed previously

**Introduction of an artificial gene for Irs2 into  $\beta$ -cells that upregulates Irs2 expression.**

Gene therapy is a general method for correcting errors in gene expression in various cells. An artificial gene encoding Irs2 can be introduced in to  $\beta$ -cells to increase the expression of Irs2 and prevent diabetes. The gene can be constitutively active or it might contain regulatory elements that control its expression. Different delivery systems might be used. Adenovirus, HIV, lentivirus or other methods might provide ways of upregulating Irs2 in  $\beta$ -cells or other cell of the body. The upregulation of the Irs2 gene might be accomplished during incubation

of isolated human islets immediately after isolation from human donors. These islets that are engineered to express Irs2 can then be used for transplantation. Upregulation of Irs2 in murine islets promotes their function during transplantation, suggesting that such a method might work in humans.

**Introduction of a regulatory sequence that targets the endogenous gene for Irs2 so that it is upregulated in  $\beta$ -cells.**

The expression of genes is well known to be controlled by regulatory elements that bind various transcription factors. These factors are regulated by other signaling system. One way to upregulate a gene is to add a regulatory element to the gene so that its activity is controlled in a new way. There are various strong promoter available that can be inserted in front of Irs2 that will increase its expression. By targeting these elements to specific cells Irs2 expression can be enhanced.

**Introduction of an artificial gene for Irs2 into isolated  $\beta$ -cells or pluripotent stem cells that are subsequently put back into patients.**

The introduction of an Irs2 gene into cells in the body might be difficult. In this case it is easier to remove the islets from the body, treat them with DNA that will alter the expression of the Irs2 gene, perhaps by introducing more copies of the *irs2* gene, or by altering the regulatory region of the Irs2 gene by homologous recombination. These engineered cells can then be replaced into the body to cure diabetes. Alternatively, islets might be isolated from other people, ideally related people, but also from unrelated people. The expression of Irs2 can then be upregulated by altering the expression of the gene by the methods described above and the cells can be replaced in the patient. In another possible approach, islets might be obtained from other mammals and expression of Irs2 increased by genetic means as described above. These might be pig islets, cow islet, monkey islets or even appropriate stem cells. The islets might have been modified already to be acceptable for transplantation into people. Then the modified islets expressing Irs2 can be transplanted in to the patient or placed into an appropriate biocompatible container to avoid rejection.





Attorney Docket No. 66112-999

EV 064 965 626 US

**Methods of identifying and using Irs2 promoting compounds to reverse catabolism during acute trauma.**

A major problem during acute trauma is that insulin resistance and decreased insulin secretion leads to massive catabolism. Using drugs that promote Irs2 function will reverse these effects.

**Methods of identifying and using Irs2 promoting compounds to prevent insulin resistance and diabetes in obese people**

A major problem with obesity is that peripheral tissues become insulin resistant; and if the  $\beta$ -cells fail to make enough insulin to overcome the insulin resistance then diabetes develops. This can be treated with compounds that upregulate Irs2 in  $\beta$ -cells and/or peripheral tissues. Upregulating Irs2 in  $\beta$ -cells promotes better glucose detection and insulin secretion, and upregulating Irs2 in peripheral tissues reduces the insulin requirements. This would reduce the incidence of life threatening complications.

**Methods of upregulating a gene that upregulates Irs2 levels and function in  $\beta$ -cells and other cell types.**

Like other genes, Irs2 is regulated by transcription factors. One way to increase Irs2 expression is to increase the activity of the transcription factors that stimulate the transcription of the Irs2 genes. Such compounds can be easily identified through the use of cell based screens, as previously described.

**Methods of downregulating a gene that downregulates Irs2 levels in  $\beta$ -cells.**

Like other genes, Irs2 is regulated by transcription factors. Gene products that might down regulate Irs2 protein or RNA levels can be targeted for inhibition to prevent this negative effect.

**Methods of identifying and using compounds that inhibit the inhibition or destruction of Irs2 in  $\beta$ -cells by the immune system.**

Type 1 diabetes is an autoimmune disease. Leukocytes are attracted to islets by  $\beta$ -cell autoantigens. Once they have migrated to pancreatic islets, the leukocytes then attack and destroy the  $\beta$ -cells through cell-cell contacts or by releasing proinflammatory cytokines that promote  $\beta$ -cells death. Death of a  $\beta$ -cells is thought to occur through mechanisms that are common to other cells, such as activation of the caspase cascade including the cleavage and activation of caspase -3. Irs2 signaling generally inhibits apoptosis of many cells types, including  $\beta$ -cells, by promoting phosphorylation of BAD and dissociation of BCL1 that inhibits a cascade the culminates in caspase-3 cleavage and activation. One of the ways that leukocytes prepare cells for rapid killing is to remove functional Irs2 by either inhibiting its function or promoting its degradation. Compounds that inhibit degradation of Irs2 and inhibit its serine phosphorylation will oppose the killing effects leukocytes.

***Methods and compounds that protect the tyrosine phosphorylation state of Irs2 in  $\beta$ -cells.***

Irs2 mediates signals that promote functional growth and survival of  $\beta$ -cells through tyrosine phosphorylation mediated by the IGF1 receptor, insulin receptor or other receptors coupled to tyrosine kinases. Phosphatases dephosphorylate Irs proteins and inhibit these positive effects. Compounds that inhibit specific phosphatase activities in  $\beta$ -cells will upregulate Irs2 function and promote  $\beta$ -cells function. General screening methods are well known that can be used to find drugs with the proper phosphatase inhibiting effects. For example PTP1B is an example of one such phosphatase that can be targeted for inhibition, and there are other important phosphatases in  $\beta$ -cells as well as in other cell types.

**Methods and compounds that inhibit ubiquitination of Irs2 in  $\beta$ -cells.**

Irs2 proteins are targeted for degradation upon ubiquitination. Therefore, compounds that inhibit the interaction between Irs2 and ubiquitin transferase complexes or inhibit the accessibility of residues that get ubiquitinated will prolong the half life of Irs2 and thereby enhance its signaling capacity.

Attorney Docket No. 66112-999

EV 064 965 626 US

**Methods and compounds that activate or inhibit serine, threonine and tyrosine phosphorylation of Irs2 in  $\beta$ -cells, neurons, or other cell types that are Irs2 sensitive for growth, function or survival.**

Irs2 proteins are targets for phosphorylation by serine, threonine and tyrosine kinases. Therefore, compounds that inhibit or stimulate phosphorylation of Irs2 will modulate Irs2 cellular function in a therapeutically useful manner. Such functions of Irs2 will include its ability to interact with (bind to) other proteins involved in various signal transduction cascades that are beneficial for the treatment of human diseases such as type II diabetes, neurodegenerative diseases such as Alzheimer's disease, cardiovascular diseases, peripheral neuropathy, vascular disease, retinopathies, macular degeneration, and the like.

#### References

- 1.. White,M.F., Maron,R. & Kahn,C.R. Insulin rapidly stimulates tyrosine phosphorylation of a Mr-185,000 protein in intact cells. *Nature* 318, 183-186 (1985). Ref ID: 179
2. Sun,X.J. *et al.* Structure of the insulin receptor substrate IRS-1 defines a unique signal transduction protein. *Nature* 352, 73-77 (1991). Ref ID: 133
3. Sun,X.J. *et al.* Role of IRS-2 in insulin and cytokine signalling. *Nature* 377, 173-177 (1995). Ref ID: 89
4. Withers,D.J. *et al.* Disruption of IRS-2 causes type 2 diabetes in mice. *Nature* 391, 900-904 (1998). Ref ID: 52
5. White,M.F. IRS proteins and the common path to diabetes. *Am. J. Physiol Endocrinol. Metab* 283, E413-E422 (2002). Ref ID: 6

#### Related Patents

1. Kahn, C.R., White, M.F., Rothenberg, P.L. Isolated DNA encoding an insulin receptor substrate. US patent No:5,620,200. Filed 10/15/92. Issued 11/9/93.
2. Kahn, C.R., White, M.F., Rothenberg, P.L. Insulin receptor substrate. US patent No:5,621,075. Filed 07/21/93. Issued 04/15/97.
3. White, M.F., Sun, X.J., Pierce, J.H. DNA encoding an insulin receptor substrate. Us patent No:5,858,701. Filed 10/03/94. Issued 01/12/99.